

# Trends of the Epidemiology of Candidemia in Switzerland: A 15-Year FUNGINOS Survey

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**Background.** The increasing incidence of candidemia and emergence of drug-resistant *Candida* species are major concerns worldwide. Long-term surveillance studies are needed.

**Methods.** The Fungal Infection Network of Switzerland (FUNGINOS) conducted a 15-year (2004–2018), nationwide, epidemiological study of candidemia. Hospital-based incidence of candidemia, *Candida* species distribution, antifungal susceptibility, and consumption were stratified in 3 periods (2004–2008, 2009–2013, 2014–2018). Population-based incidence over the period 2009–2018 derived from the Swiss Antibiotic Resistance Surveillance System (ANRESIS).

**Results.** A total of 2273 *Candida* blood isolates were studied. Population and hospital-based annual incidence of candidemia increased from 2.96 to 4.20/100 000 inhabitants ( $P = .022$ ) and 0.86 to 0.99/10 000 patient-days ( $P = .124$ ), respectively. The proportion of *Candida albicans* decreased significantly from 60% to 53% ( $P = .0023$ ), whereas *Candida glabrata* increased from 18% to 27% ( $P < .0001$ ). Other non-*albicans* *Candida* species remained stable. *Candida glabrata* bloodstream infections occurred predominantly in the age group 18–40 and above 65 years. A higher proportional increase of *C glabrata* was recorded in wards (18% to 29%,  $P < .0001$ ) versus intensive care units (19% to 24%,  $P = .22$ ). According to Clinical and Laboratory Standards Institute, nonsusceptibility to fluconazole in *C albicans* was observed in 1% of isolates, and anidulafungin and micafungin nonsusceptibility was observed in 2% of *C albicans* and *C glabrata*. Fluconazole consumption, the most frequently used antifungal, remained stable, whereas use of mold-active triazoles and echinocandins increased significantly in the last decade ( $P < .0001$ ).

**Conclusions.** Over the 15-year period, the incidence of candidemia increased. A species shift toward *C glabrata* was recently observed, concurring with increased consumption of mold-active triazoles.

**Keywords.** antifungals; candida; candidemia; epidemiology; resistance.

*Candida* species are the most common cause of nosocomial fungal infections [1]. Candidemia is associated with substantial morbidity, mortality, and increased healthcare costs [2, 3].

The worldwide incidence of candidemia is difficult to assess, and long-term population-based surveillance data are available from few countries. Reported incidence rates vary significantly between 3.2 and 8.4 episodes/100.000 inhabitants [4–9].

In a nationwide survey of candidemia performed by the Fungal Infection Network of Switzerland (FUNGINOS) between 1991 and 2000, hospital-based incidence rates remained unchanged over the 10-year period [10]. Over the last 2 decades, new antifungal agents and new management strategies such as antifungal prophylaxis and pre-emptive therapy using triazoles or echinocandins have been recommended in high-risk hospital populations, in particular patients with hematological malignancies and critically ill patients [1]. Their larger use may have influenced the *Candida* species distribution and antifungal susceptibility. Although *Candida albicans* has been the worldwide predominant species during decades, a shift to *Candida*

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species with reduced fluconazole susceptibility, in particular *Candida glabrata*, has been reported from many countries [11, 12]. In addition, there are increasing reports of echinocandin-resistant *Candida* infections [13–15]. In Switzerland, no shift to resistant *Candida* species was observed in the FUNGINOS hospitals over the period 1991–2009 [10, 16]. To evaluate the trends in the epidemiology and antifungal drug susceptibility of candidemia in Switzerland, FUNGINOS conducted a prospective study over 15 years from 2004 to 2018.

## METHODS

The present prospective survey of candidemia in Switzerland was conducted in 5 university and 2 tertiary care university-affiliated hospitals of the FUNGINOS research network.

### Hospital and Population-Based Surveillance Over the Period 2004–2018

For hospital-based surveillance, epidemiological and microbiological data of the 7 participating hospitals were included over 2004–2018 and stratified in 3 periods (2004–2008, 2009–2013, 2014–2018). These institutions are distributed across the country and play a key role in the national healthcare system. All adult hematopoietic stem cell and solid organ transplantations are performed in these 7 hospitals. Five of seven surveyed hospitals include affiliated pediatric centers.

For population-based surveillance, microbiological data were included from the Swiss Antibiotic Resistance Surveillance System (ANRESIS) from 2009 to 2018. The ANRESIS program centralizes antibiotic and antifungal resistance data of microorganisms from a representative selection of clinical microbiology laboratories [17]. From 2009 to 2018, the annual coverage of national laboratories by ANRESIS increased from 60.9% to 80.6%. To calculate the incidence rates of candidemia per 100 000 inhabitants, annual population data were extracted from the Federal Statistical Office database and were corrected according to the reported coverage by ANRESIS [18]. The study has been approved by the Ethical Committee of the Lausanne University Hospital as the FUNGINOS national coordinating center.

### Study Variables

The following variables were recorded by questionnaire survey on a yearly basis: hospital activities, number and species of the 10 most frequent bloodstream pathogens, *Candida* isolates from blood cultures, age and ward distribution of patients with candidemia, and consumption of antibiotics and antifungals. A *Candida* isolate from at least 1 blood culture set was defined as candidemia. Multiple *Candida* isolates of the same species from the same patient were considered as different episodes of candidemia if they occurred more than 4 weeks apart [19]. The annual questionnaires were distributed to local investigators (infectious diseases specialist(s) and clinical microbiologist(s)) at each hospital. The FUNGINOS Data Review Committee

checked data for completeness and consistency and addressed queries to centers. Data on hematopoietic stem cell and solid organ transplantations derived from the Federal Office of Public Health [20].

Consumption of antimicrobial agents was calculated in Defined Daily Doses (DDD) according to the 2021 Anatomical Therapeutic Chemical/ Defined Daily Dose (ATC/DDD) Index of the World Health Organization (WHO), except for fluconazole, amphotericin B, and posaconazole. For fluconazole, DDDs were calculated on a 0.4 grams basis instead of 0.2 grams, reflecting the dose recommended in severe systemic infections. For liposomal amphotericin B, DDDs were calculated on a 0.21 grams basis (3 mg/kg for a body weight of 70 kg). Posaconazole tablets and intravenous formulations were approved in Switzerland since mid-2015. Since the licensed maintenance dose of these formulations is 300 mg/day compared with 600 mg/day for the oral suspension, DDDs for posaconazole were calculated on a 0.6 grams and 0.3 grams basis before and after mid-2015, respectively.

### *Candida* Species Identification and Antifungal Susceptibility Testing

The 7 microbiology laboratories affiliated with participating hospitals used automated blood culture systems (Bactec [Becton Dickinson, Sparks, MD] or BacT/Alert [bioMérieux, Marcy l'Etoile, France]).

Over the study period 2004–2013, the *Candida* bloodstream isolates were centralized to the FUNGINOS mycology reference laboratory, Institute of Microbiology, Lausanne University Hospital (Centre hospitalier universitaire vaudois [CHUV]). *Candida* species were identified by standard biochemical assays in a test gallery (ATB ID 32 C(R); bioMérieux) and by Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry. In case of discordant identification between center and reference laboratory, molecular identification was performed by polymerase chain reaction amplification and sequencing of the D1/D2 region of the large subunit of the 28S ribosomal RNA gene (28S rDNA). Antifungal susceptibility testing was performed by microtiter broth dilution method using the Sensititre YeastOne test panel (TREK Diagnostic System, Cleveland, OH). Susceptibility testing included fluconazole, voriconazole, caspofungin, and amphotericin B over 2004–2013. Posaconazole was tested after 2005 and anidulafungin and micafungin were tested after 2010. Over 2014–2018, species identification was performed at local laboratories and susceptibility data were extracted from ANRESIS database. *Candida* species identification and susceptibility testing at local laboratories were performed by MALDI-TOF and Sensititre YeastOne or Etest, respectively. One center used VITEK (bioMérieux) for susceptibility testing. Only isolates with available minimum inhibitory concentration (MIC) were included. Interpretation (or reinterpretation) of antifungal susceptibility was performed according to Clinical and Laboratory Standards Institute (CLSI) document M60-Ed2.

## Statistical Analysis

Continuous variables were compared using Student's *t* test or Mann-Whitney *U* test, and proportions were compared using  $\chi^2$  test or Fisher's exact test, as appropriate. Changes in *Candida* species distribution over time were evaluated with the  $\chi^2$  test for trend. Linear trends over time were analyzed with the Poisson regression model. All *P* values were based on 2-tailed tests of significance (*P* < .05). Statistical analysis was performed using SPSS software, version 22 (IBM SPSS Statistics for Windows, Armonk, NY).

## RESULTS

### Hospital Characteristics and Patient Care Activities Over the Period 2004–2018

The number of hospital beds, patient-days, admissions, and clinical activities at high risk for candidemia from the 7 participating institutions over the 5-year time periods 2004–2008, 2009–2013, and 2014–2018 are summarized in Table 1. The number of beds, admissions, and patient-days increased significantly over the 15-year period, whereas the length of hospital stay decreased significantly (*P* < .0001). Mean annual hematopoietic stem cell and solid organ transplantations increased by 75% and 26%, respectively.

### Trends of Bloodstream Infections

Data on the most frequent isolates in bloodstream infections (BSIs) were available for 5 hospitals. The top 10 ranking of BSIs remained stable over 15 years with the exception of a proportional increase of *Enterococcus* spp and a decrease of *Streptococcus pneumoniae*. Among the 10 most frequently reported bloodstream pathogens, *Candida* species accounted for 2.9% in 2004–2008, 3.6% in 2009–2013, and 2.1% in 2014–2018. In 2014–2018, *Candida* BSI ranked 10th (range, 9–11) (Supplemental Table 1).

### *Candida* Species Incidence and Distribution

A total of 2273 *Candida* blood isolates were documented in the 7 centers over the period 2004–2018. A trend for increasing hospital-based incidence of candidemia was found in the last

5 years with 0.86 (standard deviation [SD] = 0.11) and 0.81 (SD = 0.12) per 10 000 patient-days in 2004–2008 and 2009–2013 and 0.99 (SD = 0.09) in 2014–2018 (*P* = .124) (Figure 1A). Consistently, population-based incidence of candidemia from the nation-wide retrospective ANRESIS surveillance increased significantly over the last 5 years from 2.96 (SD = 0.37) per 100 000 inhabitants in 2009–2013 to 4.20 (SD = 0.47) in 2014–2018 (*P* = .022).

Hospital-based incidence rates of candidemia per 10 000 patient-days remained stable for *C. albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, and the other *Candida* species, whereas it increased significantly for *C. glabrata* from 0.15 per 10 000 patient-days in 2004–2008 and 2009–2013 to 0.27 in 2014–2018 (*P* = .008) (Figure 1A).

Over the 15-year study period, *C. albicans* was the most frequent species (58%), followed by *C. glabrata* (21%), *C. tropicalis*, and *C. parapsilosis* (each 5%). *Candida krusei* remained rare with 3%. Eight percent of all isolates belonged to other *Candida* spp. No *Candida auris* was isolated during the study period. The proportion of *C. albicans* decreased significantly from 60% in 2004–2008 to 53% in 2014–2018 (*P* = .0023). By contrast, the proportion of *C. glabrata* increased from 18% to 27% (*P* < .0001) (Figure 1B). No change was observed in the proportions of other *Candida* species.

### *Candida* Species Distribution According to Patients' Age and Location in the Hospital

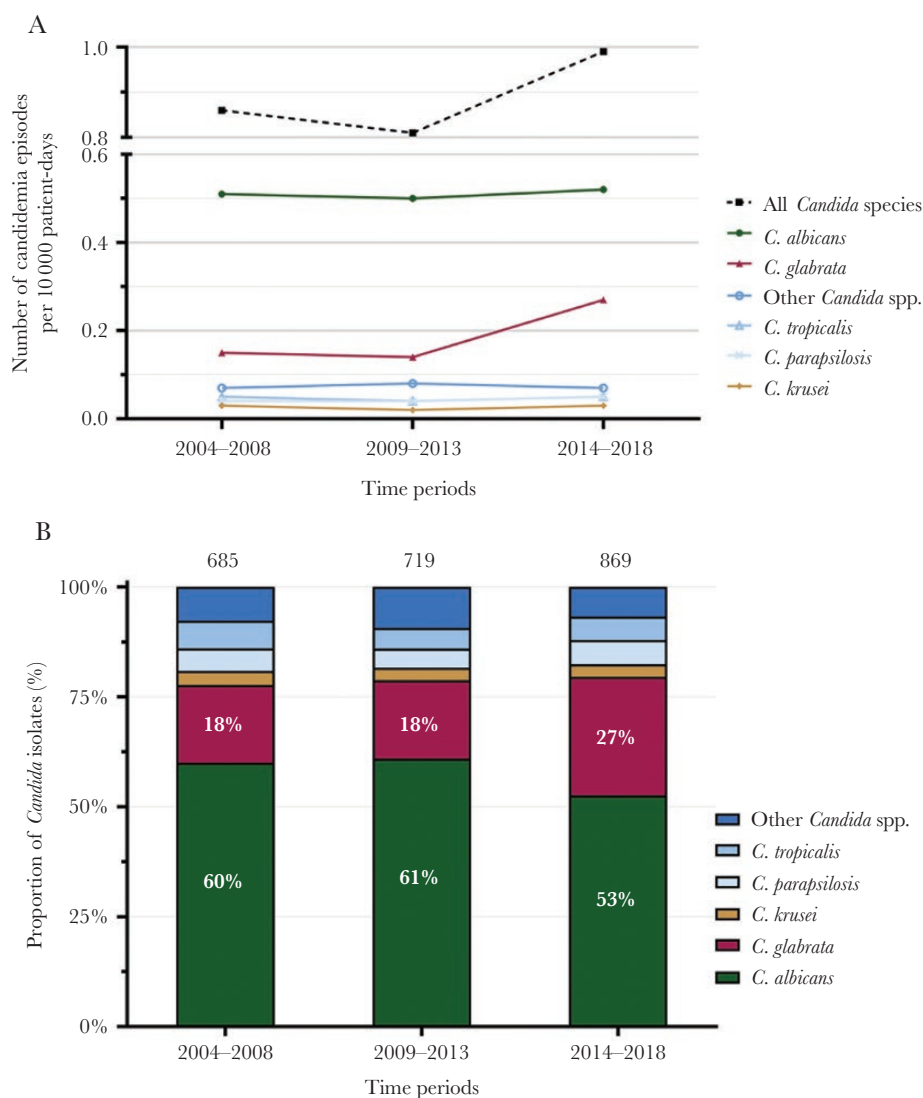
Data on *Candida* species distribution according to patients' age were available from 4 hospitals, representing 52% of all candidemias. The highest proportion of *C. glabrata* (23%) was found in the age group 18–40 and above 65 years (Figure 2A). *Candida tropicalis* and other *Candida* spp occurred proportionally more frequently in the age group 18–40 years. Although only a limited number of isolates of patients below 18 years have been investigated, a tendency to a higher proportion of *C. parapsilosis* was observed in this age group.

Data on patients' hospital location at the time of candidemia were available from all 7 hospitals. A higher proportional increase of *C. glabrata* was recorded in wards, from 18% in

**Table 1. Hospital Activities in the Seven Participating Hospitals Over the Period 2004–2018**

	Years			P Value (r)
	2004–2008	2009–2013	2014–2018	
Admissions	203 939 (16 456)	233 509 (5529)	271 017 (9136)	<i>P</i> < .0001, <i>r</i> = 0.92
Patient-days	1 596 485 (49 017)	1 768 829 (16 784)	1 753 755 (40 072)	<i>P</i> = .002, <i>r</i> = 0.74
Length of stay, days	7.9 (0.4)	7.6 (0.2)	6.5 (0.1)	<i>P</i> < .0001, <i>r</i> = –0.87
Beds	5067 (192)	5492 (110)	5530 (396)	<i>P</i> = .029, <i>r</i> = 0.56
Solid organ transplantations	454 (20.3)	494 (16.6)	571 (39.2)	<i>P</i> < .0001, <i>r</i> = 0.86
Hematopoietic stem cell transplantations	409 (26.2)	544 (41.3)	719 (53.8)	<i>P</i> < .0001, <i>r</i> = 0.95
Allogeneic	135 (19.4)	182 (18.3)	247 (12.8)	
Autologous	275 (15.7)	362 (24.1)	472 (42.7)	

Data are reported as mean annual numbers and standard deviation.



**Figure 1.** (A) Annual incidence of candidemia per 10 000 patient days in the 7 hospitals over the 3 time periods 2004–2008, 2009–2013, and 2014–2018. (B) Species distribution of *Candida* bloodstream isolates. Total number of *Candida* isolates per time period are indicated at the top.

2004–2008 to 29% in 2014–2018 ( $P < .0001$ ), than in intensive care units, from 19% to 24% ( $P = .22$ ) (Figure 2B).

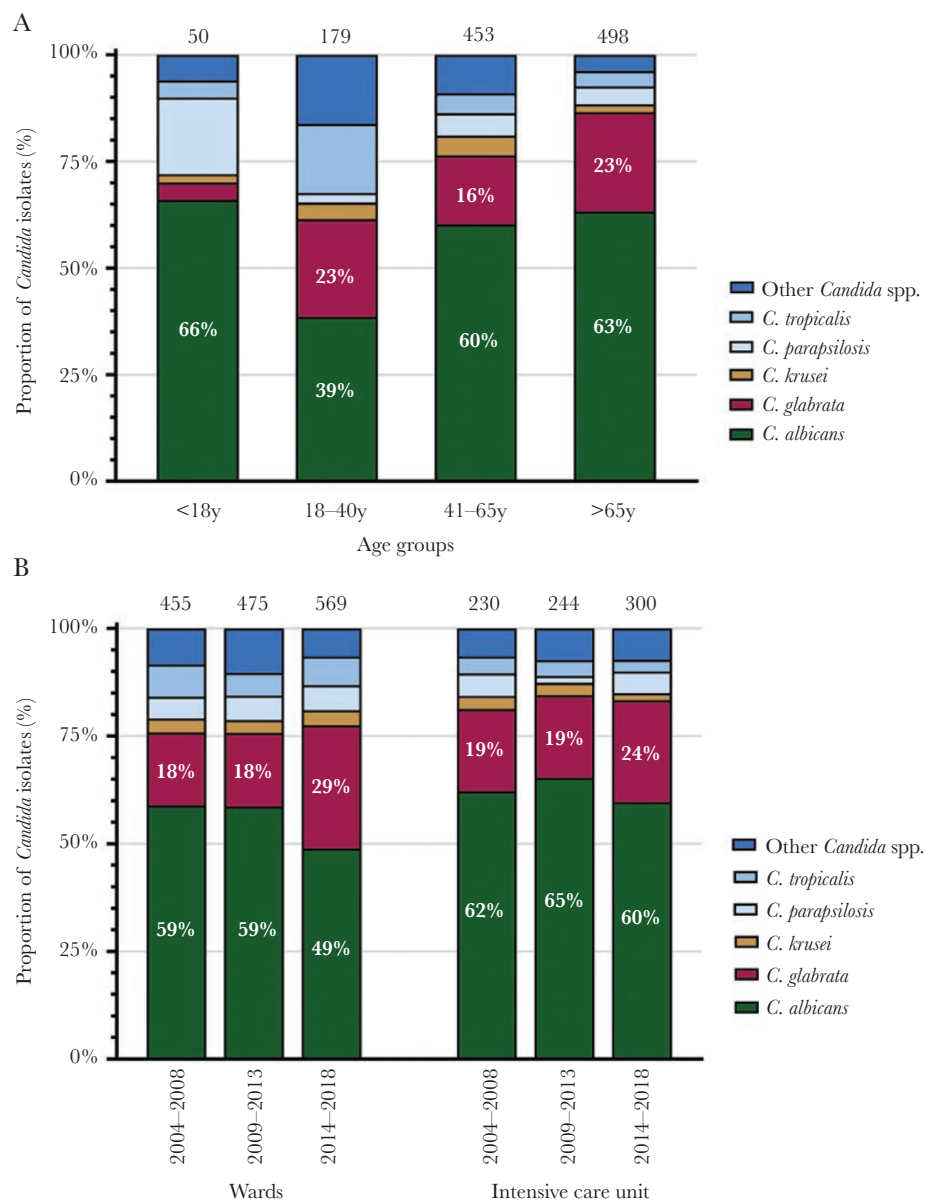
#### Antifungal Susceptibility Testing According to Clinical and Laboratory Standards Institute

Availability of susceptibility data varied during the study period. Over the whole study period, 88% ( $n = 1835$ ) of *Candida* isolates (*C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*) were tested for fluconazole, 80% ( $n = 1681$ ) were tested for voriconazole, 63% ( $n = 1319$ ) were tested for posaconazole, 81% ( $n = 1697$ ) were tested for amphotericin B, 75% ( $n = 1564$ ) were tested for caspofungin, 30% ( $n = 626$ ) were tested for anidulafungin, and 32% ( $n = 662$ ) were tested for micafungin. Overall, 33% ( $n = 207$ ) of all tested *Candida* isolates in 2014–2018 were classified as nonsusceptible (ie, susceptible-dose-dependent or resistant) to fluconazole, mainly

due to the high proportion of *C. glabrata* (Table 2). Fluconazole nonsusceptibility among *C. albicans* remained at 1% over the 15-year period. In *C. parapsilosis*, fluconazole nonsusceptibility fluctuated from 6% to 7% to 4% from 2004–2008 to 2009–2013 and 2014–2018, respectively. Micafungin and anidulafungin nonsusceptibility in *C. albicans* and *C. glabrata* remained below 2%.

#### Antibiotic and Antifungal Drugs Consumption

The consumption of broad-spectrum antibiotics with anti-*Pseudomonas aeruginosa* activity increased over the 15 years in the 7 hospitals ( $P < .0001$ ). The overall antifungal drug consumption increased from 2.12 to 3.65 DDD per 100 patient-days from 2004 to 2011, and it remained stable afterwards (Figure 3A). Fluconazole use remained stable since 2007 (Figure 3B). Consumption of mold-active triazoles (voriconazole,



**Figure 2.** (A) Species distribution of *Candida* bloodstream isolates according to patients' age over 2004–2018 (4 hospitals). Total number of *Candida* isolates per age group are indicated at the top. (B) Species distribution of *Candida* bloodstream isolates according to patients' location in the hospital over 2004–2018 (7 hospitals). Total number of *Candida* isolates per time period and ward are indicated at the top. Other *Candida* spp included (total numbers): *Candida dubliniensis* (n = 65), *C. lusitanae* (n = 20), *Candida pelliculosa* (n = 13), *Candida kefyr* (n = 11), *Candida guilliermondii* (n = 8), *C. norvegensis* (n = 8), *Candida africana* (n = 5), *Candida orthopsilosis* (n = 4), *Candida nivariensis* (n = 4), *Candida fabianii* (n = 3), *Candida inconspicua* (n = 2), *Candida palmioleophila* (n = 2), *Candida rugosa* (n = 1), *Candida pulcherrima* (n = 1).

posaconazole, isavuconazole) increased from 0.37 to 1.21 DDD per 100 patient-days during 2004–2018 ( $P < .0001$ ) (Figure 3C). Voriconazole use increased from 2004 to 2007, remained stable until 2015, and decreased thereafter. Posaconazole consumption overtook voriconazole consumption in 2016 (Figure 3C). Echinocandin use increased from 0.2 to 0.6 DDD per 100 patient-days from 2004 to 2012 ( $P < .0001$ ) and remained stable thereafter. Liposomal amphotericin B consumption increased ( $P < .0001$ ), whereas amphotericin deoxycholate decreased ( $P < .0001$ ) during 2004–2018 (data not shown).

## DISCUSSION

This FUNGINOS study provides a longitudinal overview of the secular trends of candidemia associated with patient care activities. This survey, together with the previous 10-year FUNGINOS study, is representative for the entire country over a 30-year period and constitutes one of the largest contemporary worldwide series of candidemia. Our analysis revealed 3 major findings. The incidence of candidemia showed a significant increase. Mold-active triazole and echinocandin consumption increased significantly. A shift toward *C. glabrata*



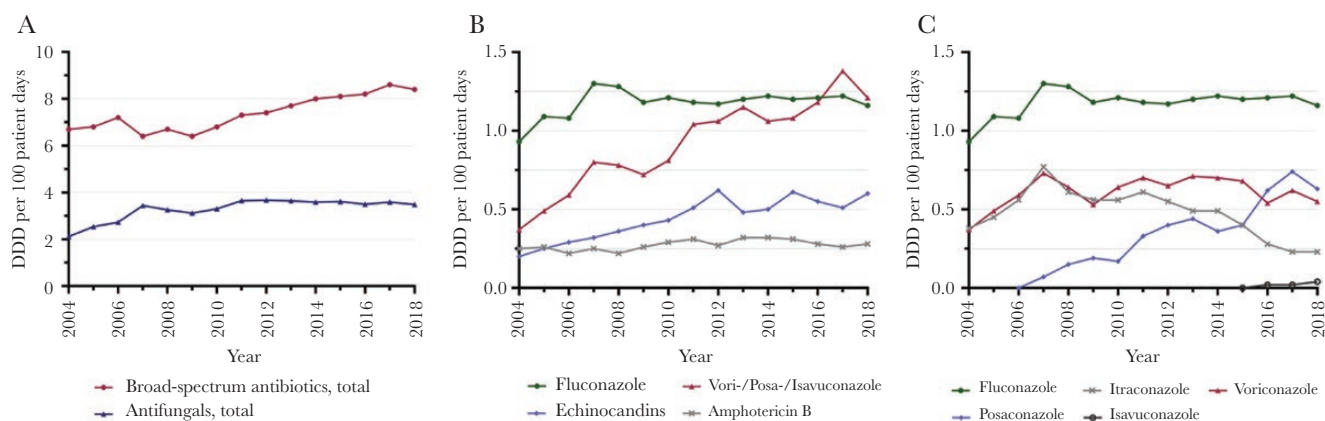
**Table 2. Susceptibility of *Candida* Bloodstream Isolates to Antifungal Drugs According to CLSI Document M60-Ed2**

Species	S or WT*				I				SDD				R or Non-WT**				No. of Isolates Tested			
	2004–2008	2009–2013	2014–2018	2014–2018	2009–2013	2004–2008	2014–2018	2014–2018	2009–2013	2004–2008	2014–2018	2014–2018	2009–2013	2004–2008	2014–2018	2014–2018	2009–2013	2004–2008	2014–2018	2014–2018
<i>Candida albicans</i>																				
Fluconazole	99%	99%	99%	99%	-	-	-	0%	0%	-	0%	1%	1%	1%	0%	0%	411	426	330	330
Voriconazole	99%	99%	99%	99%	0%	0%	0%	0%	-	-	-	-	0%	0%	0%	0%	411	428	277	277
Posaconazole	99%*	98%*	96%*	96%*	-	-	-	-	-	-	-	1%**	2%**	2%**	4%**	4%**	227	426	214	214
Caspofungin	100%	99%	98%	98%	0%	0%	1%	1%	-	-	-	0%	0%	0%	1%	1%	409	426	150	150
Amphotericin B	100%*	100%*	100%*	100%*	-	-	-	-	-	-	-	0%**	0%**	0%**	0%**	0%**	399	425	214	214
Anidulafungin	<sup>a</sup>	99%	99%	99%	<sup>a</sup>	0%	0%	0%	-	-	-	<sup>a</sup>	1%	1%	1%	0	141	212	212	212
Micafungin	<sup>a</sup>	100%	98%	98%	<sup>a</sup>	0%	0%	0%	-	-	-	<sup>a</sup>	0%	0%	2%	0	218	176	176	176
<i>Candida glabrata</i>																				
Fluconazole	-	-	-	-	-	-	-	-	90%	-	90%	91%	10%	8%	9%	117	124	176	176	176
Voriconazole	79%	61%	70.5%*	70.5%*	-	-	-	-	-	-	-	21%**	39%**	29.5%**	29.5%**	117	124	44	44	44
Posaconazole	92.5%*	70%*	86%*	86%*	-	-	-	-	-	-	-	7.5%**	30%**	14%**	14%**	67	124	43	43	43
Caspofungin	91%	94%	95%	95%	8%	6%	2%	2%	-	-	-	1%	0%	3%	3%	117	124	104	104	104
Amphotericin B	100%*	100%*	100%*	100%*	-	-	-	-	-	-	-	0%**	0%**	0%**	0%**	117	124	147	147	147
Anidulafungin	<sup>a</sup>	100%	98%	98%	<sup>a</sup>	0%	1%	1%	-	-	-	<sup>a</sup>	0%	1%	1%	0	40	124	124	124
Micafungin	<sup>a</sup>	100%	98%	98%	<sup>a</sup>	0%	2%	2%	-	-	-	<sup>a</sup>	0%	0%	0%	0	75	107	107	107
<i>Candida krusei</i>																				
Fluconazole	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Voriconazole	81%	100%	91%	91%	14%	0%	9%	9%	-	-	-	5%	0%	0%	0%	21	20	11	11	11
Posaconazole	100%*	100%*	100%*	100%*	-	-	-	-	-	-	-	0%**	0%**	0%**	0%**	13	20	3	3	3
Caspofungin	38%	85%	78%	78%	43%	15%	22%	22%	-	-	-	19%	0%	0%	0%	21	20	9	9	9
Amphotericin B	100%*	100%*	100%*	100%*	-	-	-	-	-	-	-	0%**	0%**	0%**	0%**	21	20	16	16	16
Anidulafungin	<sup>a</sup>	100%	100%	100%	<sup>a</sup>	0%	0%	0%	-	-	-	<sup>a</sup>	0%	0%	0%	0	6	15	15	15
Micafungin	<sup>a</sup>	100%	100%	100%	<sup>a</sup>	0%	0%	0%	-	-	-	<sup>a</sup>	0%	0%	0%	0	12	4	4	4
<i>Candida parapsilosis</i>																				
Fluconazole	94%	93%	96%	96%	-	-	-	-	6%	-	6%	0%	0%	7%	4%	35	30	50	50	50
Voriconazole	100%	100%	95%	95%	0%	0%	2%	2%	-	-	-	0%	0%	0%	2%	35	30	44	44	44
Posaconazole	100%*	97%*	97.5%*	97.5%*	-	-	-	-	-	-	-	0%**	3%**	2.5%**	2.5%**	24	30	40	40	40
Caspofungin	100%	100%	100%	100%	0%	0%	0%	0%	-	-	-	0%	0%	0%	0%	35	30	19	19	19
Amphotericin B	100%*	100%*	97.5%*	97.5%*	-	-	-	-	-	-	-	0%**	0%**	2.5%**	2.5%**	35	30	40	40	40
Anidulafungin	<sup>a</sup>	100%	97%	97%	<sup>a</sup>	0%	3%	3%	-	-	-	<sup>a</sup>	0%	0%	0%	0	11	39	39	39
Micafungin	<sup>a</sup>	100%	97%	97%	<sup>a</sup>	0%	3%	3%	-	-	-	<sup>a</sup>	0%	0%	0%	0	14	34	34	34
<i>Candida tropicalis</i>																				
Fluconazole	90%	82%	80%	80%	-	-	-	-	5%	-	5%	9%	12%	11%	11%	42	33	45	45	45
Voriconazole	83%	82%	75%	75%	14%	6%	16%	16%	-	-	-	2%	12%	9%	9%	42	33	44	44	44
Posaconazole	75%*	70%*	74%*	74%*	-	-	-	-	-	-	-	25%**	30%**	26%**	26%**	20	33	35	35	35
Caspofungin	100%	91%	96%	96%	0%	6%	4%	4%	-	-	-	0%	3%	0%	0%	42	33	25	25	25
Amphotericin B	100%*	100%*	100%*	100%*	-	-	-	-	-	-	-	0%**	0%**	0%**	0%**	41	33	35	35	35
Anidulafungin	<sup>a</sup>	100%	97%	97%	<sup>a</sup>	0%	3%	3%	-	-	-	<sup>a</sup>	0%	0%	0%	0	6	32	32	32
Micafungin	<sup>a</sup>	100%	100%	100%	<sup>a</sup>	0%	0%	0%	-	-	-	<sup>a</sup>	0%	0%	0%	0	12	10	10	10

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; I, intermediate; R, resistant; S, susceptible; SDD, susceptible, dose-dependent; WT, wild type.

Classification according to CLSI clinical breakpoints (CBP). In the absence of established CBP, CLSI epidemiological cutoff values (ECV) were used for discrimination between WT\* and non-WT\*\* isolates (CLSI document M59-Ed3).

<sup>a</sup>Isolates were not tested for the specific drug.



**Figure 3.** (A) Annual consumption of broad-spectrum antibiotics and antifungals in Defined Daily Doses (DDDs) per 100 patient days over 2004–2018. (B) Annual consumption of antifungals in DDDs per 100 patient days over 2004–2018. (C) Annual consumption of azoles in DDDs per 100 patient days over 2004–2018. Data of 7 hospitals are reported. Broad-spectrum antibiotics include the following: cefepime, piperacillin/tazobactam, imipenem, and meropenem. Antifungals include fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole, amphotericin B deoxycholate, liposomal amphotericin B, caspofungin, and anidulafungin. The DDDs were defined as follows: cefepime 4 grams, piperacillin/tazobactam 14 grams, imipenem 2 grams, meropenem 3 grams; fluconazole 0.4 grams, itraconazole 0.2 grams, voriconazole 0.4 grams, posaconazole 0.3–0.6 grams, isavuconazole 0.2 grams, amphotericin B deoxycholate 0.07 grams, liposomal amphotericin B 0.21 grams, caspofungin 0.05 grams, and anidulafungin 0.2 grams.

was observed after 2013, representing 27% of all candidemias in 2014–2018.

The population-based candidemia incidence in our study is in line with reports from Sweden (4.7/100 000, 2016) and England (3.2/100 000, 2018), whereas it is higher than that reported in Australia (2.41/100 000, 2014–2015), and lower than in Denmark (8.38/100 000, 2013–2015), Spain (8.1/100 000, 2010–2011), and the United States (8.2/100 000, 2013–2017) [4–8, 11]. Multiple reasons may explain large differences in population-based candidemia incidences, which may be influenced by geographical and ecological factors, variability in monitoring and reporting systems, studied patient populations, infection prevention and control strategies, as well as clinical management and antimicrobial use practices [21].

International comparison of hospital-based incidences of candidemia is difficult, because they highly depend on the study population and time period studied, whereas changes over time within a single country, where reporting and monitoring systems remain stable, may be more accurate. In Switzerland, hospital-based incidence rates of candidemia have been studied by FUNGINOS using standardized questionnaires since 1991. Compared with our previous survey, in which incidence rates remained unchanged, we now observed an increase of candidemia from 0.49 episodes per 10 000 patient-days to 0.99 episodes over the last 3 decades [10].

Although the *Candida* species distribution was stable over 2 decades, we observed a significant decrease of the proportion of *C. albicans* and an increase of *C. glabrata* since 2014. This observation is consistent with data from the United States as well as from Australia, Denmark, and Canada from 2004 to 2015 [5, 11, 12, 14]. The recent emergence of *C. glabrata*

infections in Switzerland has occurred concomitantly with the increased use of mold-active triazoles in the last decade. The proportion of other non-*albicans Candida* species such as *C. parapsilosis* and *C. tropicalis*, which increased in southern Europe and South America, remained stable in Switzerland, ranging 4%–6% [4, 22].

*Candida glabrata* infections occurred predominantly in patients hospitalized on wards and in the age group 18–40 years and above 65 years. This may reflect the prolonged azole exposure for prophylaxis or therapy in patients with malignant hematological diseases or undergoing transplantation [23–26].

Overall, acquired antifungal resistance in *Candida* species remains rare in Switzerland. *Candida auris* BSI has not been detected in our country in spite of a look-back analysis to exclude misidentification [27]. Although few cases of acquired echinocandin resistance associated with *FKS* mutations have been reported in Switzerland since 2009, we do not have any indication of the emergence of *FKS* mutations based on the low echinocandin MICs observed in our survey [28]. Anidulafungin and micafungin MICs according to CLSI interpretative criteria or commercial Sensititre YeastOne echinocandins epidemiological cutoff values appear sensitive and specific for identifying *FKS* mutations among *C. albicans* and *glabrata* isolates [29]. Although several countries have reported the emergence of azole resistance of *C. parapsilosis*, we did not observe such a trend in our study [30–32].

Limitations of the present study include differences in clinical practices across the different centers, the lack of individual clinical data on comorbidities, the lack of clinical data to distinguish mixed infections from candidemias with a single

species, previous antifungal drug exposure, and risk factors for candidemia or occurrence of infections due to non-*albicans* *Candida* species. Despite these limitations, this study, together with the previous FUNGINOS survey, provides one of the largest contemporary longitudinal overviews on candidemia from an entire country over a 30-year period. These data may add to contemporary initiatives such as ECMM CandiReg, which are essential for multinational surveillance of the epidemiology of *Candida* spp [33].

## CONCLUSIONS

In conclusion, after 2 decades of stable epidemiology in Switzerland, we observed a recent increase of the incidence of candidemia with emergence of *C. glabrata*, which now accounts for one fourth of bloodstream isolates. The increasing selection pressure mediated by a larger use of mold-active triazoles over the last decade most probably promoted this epidemiological shift. Continued epidemiological surveillance studies at the national level are key for monitoring the emergence of antifungal resistance and updating guidelines for antifungal therapy.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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**Author contributions.** O. M. and N. K. contributed to conception and design of the study. K.-M. A., N. K., and O. M. drafted the manuscript. K.-M. A., N. K., O. M., and F. L. contributed to data interpretation. M. O. and K.-M. A. contributed to statistical analysis and data management. All authors contributed to data collection. All authors revised the manuscript and approved the final version.

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## APPENDIX

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